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ANDREA Q. RYAN SANOFI-AVENTIS U.S. LLC 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			EXAMINER HAMA, JOANNE	
			ART UNIT 1632	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/736,801	<b>Applicant(s)</b> KLEBL ET AL.	
	<b>Examiner</b> JOANNE HAMA	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11 June 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 24-36 and 38 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 24-36 and 38 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)         | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

Applicant filed a response to the Final Action of December 11, 2009 on June 11, 2010.

Upon further consideration, the finality of the action of December 11, 2009 is withdrawn and the following Office Action addresses the rejection at hand.

Applicant filed an amendment to the claims on June 11, 2010. It is noted that Applicant must amend the claims as indicated by 37 CFR 1.121, or risk non-entry of amendments. It is noted that there are 2 claim 36s and that the second claim 36, which has been indicated as "cancelled" has text in the claim. It is noted that no text be present in cancelled claims. It is noted that the second claim 36 is interpreted to be claim 37.

Claims 1-23, 36 are cancelled. Claim 35 is amended. Claim 38 is new.

Claims 24-36, 38, drawn to a method for generating genetically modified yeast and to said yeast, are under consideration.

### **Withdrawn Rejections**

#### **35 USC § 103**

Applicant's arguments, see pages 10-14, filed June 11, 2010, with respect to the rejection of claims 24-31, 34-37 as being unpatentable over Srinivasan et al., 2000, Wilson et al., 1999, Sauer, 1987, and Buchholz et al., 1998 have been fully considered and are persuasive. Applicant indicates that Srinivasan et al. teach that their yeast with a mutation in SOD1 exhibits a specific phenotype which is different from that of the wild

Art Unit: 1632

type and is not compensated by a further endogenous mutation (Applicant's response, page 12). The rejection of claims 24-31, 34-37 has been withdrawn.

**New/Maintained Rejections**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28, 29 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record, December 11, 2009.

Applicant's arguments filed June 11, 2010 have been fully considered but they are not persuasive.

Applicant indicates that claim 28 has been amended to depend from claim 24 (Applicant's response, page 7). In response, this is not persuasive no amendment to claim 28 has been made.

Thus, the claims remain rejected.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 30, 31, 33, 34 and new claim 38 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423, previously cited, for reasons of record, April 10, 2007, January 4, 2008, August 12, 2008, March 19, 2009, December 11, 2009.

Upon further consideration, the instant rejection applies to claims 24, 30, 31, 34. Chattopadhyay et al. teach that btn1 encodes a nonessential protein that is 39% identical and 59% similar to human Cln3p. Deletion of BTN1 had no effect on mitochondrial function or the degradation of mitochondrial ATP synthase subunit c (Chattopadhyay et al., 2nd col., 1st parag.). Chattopadhyay et al. teach that disruption in btn1 (btn1 $\Delta$ ) in yeast result in yeast that have an elevated activity of the plasma membrane H<sup>+</sup>-ATPase. Microarray analysis showed that btn1 $\Delta$  yeast compensate for the altered plasma membrane H<sup>+</sup>-ATPase activity by elevating the expression of two genes, HSP30 and BTN2 (Chattopadhyay et al., abstract).

With regard to Chattopadhyay et al.'s teach not exhibiting a change of phenotype, it is noted that the yeast do not exhibit any phenotype when grown of normal media, and thus, Chattopadhyay et al.'s yeast is readable on the claims. It is noted that the yeast exhibit a phenotype when grown in a particular condition (sorbic acid).

To clarify the rejection of claim 38, with regard to claim 38 being drawn to an assay for drug screening, Chattopadhyay et al. teach that hsp30, btn2 double knockout yeast were grown in the presence of sorbic acid and that the yeast had a growth defect greater than that of the single mutant yeast (Chattopadhyay et al., page 6420, 2nd col.).

Applicant's arguments filed June 11, 2010 have been fully considered but they are not persuasive.

Applicant indicates that claim 35 has been amended to remove reference to endogenous gene in causing in the initial perturbation of the yeast cells (Applicant's response, page 8). In response, the rejection as it applies to claim 35 is withdrawn. It is noted that the rejection applied to claim 37, now cancelled, and now applies to claim 38, which is the same as claim 37.

With regard to the rejection of claim 36, it is noted that upon further consideration, the rejection is withdrawn as Chattopadhyay et al. do not specifically teach a substance that affected the function of a truncated BTN1 (it is noted that the method for making the yeast used by Chattopadhyay et al. is described in Pearce et al., 1997, Yeast, 13: 691-697, of record).

With regard to the rejection of claim 37 the rejection is withdrawn as the claims are cancelled.

Thus, the claims are rejected.

Claims 24, 30-34, 38 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Hartman et al., 2001, Science, 291: 1001-1004.

At the time of filing, Hartman et al. teach that genes buffer variation in other genes. That is, the product of gene A buffers the phenotypic consequences of variations (whether genetically, environmentally, or stochastically induced) in gene B and thus, there may be alleles of gene A that lose that buffering capacity (Hartman et

Art Unit: 1632

al., page 1002, 3<sup>rd</sup> col.). Hartman et al. teach that extreme phenotypes identify the genes that are least well buffered and the genes most relevant for their buffering, but may miss more subtle effects. What Hartman et al. view as ideal for the purpose of defining buffering relationships would be a comprehensive search of all gene combinations together with measurements that allow quantitative comparison of the degree of buffering. The results of such a study would provide a catalog of buffering relationships. New opportunities for studying the subtleties of gene interactions are enabled by entire genome sequences, microarray technologies for parallel analysis of nucleic acids and proteins, and computational methods that increase the power to analyze large amounts of data (Hartman et al., page 1003, 3<sup>rd</sup> col., to page 1004, 1<sup>st</sup> col., 1<sup>st</sup> parag.). Hartman et al. teach that it would be desirable to understand the principles and mechanisms that underlie buffering relationships. Hartman et al. teach that it makes intuitive sense that if a process is weakened, then further inactivation of that process (or of a compensatory process) would bring its activity below some debilitating threshold (Hartman et al., page 1004, 1<sup>st</sup> col., parag. under Mechanisms of Buffering). Further, Hartman et al. teach that buffering can also result from the distributed properties of systems and that negative feedback regulation is ubiquitous in biology and acts to optimize the activity of a circuit in the presence of alleles with altered activities (Hartman et al., page 1004, 2nd parag.).

To more specifically indicate how Hartman et al. anticipate the claims:

With regard to claim 24, step a being drawn to causing a heterologous expression of at least one protein or protein fragment, wherein the expression of said

Art Unit: 1632

protein or protein fragment does not produce a detectable change of the phenotype from the outside of the yeast organism, Hartman et al. teach that there is a need to study the relationship between a mutation and a gene that buffers the effect that the mutation has on the organism. This is illustrated by Hartman et al. teaching that "extreme phenotypes identify the genes that are least well buffered, and the genes most relevant for their buffering, but may miss more subtle effects," and that "what we view as ideal for the purpose of defining buffering relationships would be a comprehensive search of all the gene combinations together with measurements that allow quantitative comparison of the degree of buffering" (Hartman et al., page 1003, 3<sup>rd</sup> col.).

With regard to claim 24, step b, wherein the modified gene expression is analyzed and compensating genes are identified, Hartman et al. teach this limitation by indicating that "what we view as ideal for the purpose of defining buffering relationships would be a comprehensive search of all the gene combinations together with measurements that allow quantitative comparison of the degree of buffering" (Hartman et al., page 1003, 3<sup>rd</sup> col.) and indicate that microarrays can be used to study the subtleties of gene interaction (Hartman et al., page 1004, 1<sup>st</sup> col., line 3).

With regard to claim 24, step c, wherein the yeast is phenotyped following the reduction or elimination of the compensating genes, Hartman et al. teach that "it makes intuitive sense that if a process is weakened, the further inactivation of that process (or of a compensatory process) would bring its activity below some debilitating threshold" (Hartman et al., page 1004, 1<sup>st</sup> col., under Mechanisms of Buffering).



With regard to claim 30 being drawn to using *S. cerevisiae*, Hartman et al. teach that studies of genes that buffer other genes are carried out in a number of organisms, including yeast, *S. cerevisiae* (Hartman et al., page 1002, 2<sup>nd</sup> col., 2<sup>nd</sup> parag. to 3<sup>rd</sup> col., see also Figure 2).

With regard to claim 32 being drawn to the differentially expressed gene being less strongly expressed in control organisms and the reduction or elimination of the differential expression is carried out by enhancing expression of the differentially expressed gene, Hartman et al. teach that it makes intuitive sense that if a process is weakened, then further inactivation of that process (or of a compensatory process) would bring its activity below some debilitating threshold (Hartman et al., page 1004, 1<sup>st</sup> col., 1<sup>st</sup> parag. under Mechanisms of Buffereing).

With regard to claim 33 being drawn to elimination of the compensatory gene leading to growth inhibition, Hartman et al. teach that growth is a convenient phenotype to study buffering (Hartman et al., page 1002, 3<sup>rd</sup> col.).

Thus, the claims are rejected.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 24-29, 32-36, 38 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423 in view of Sauer, 1987, Molecular and Cellular Biology, 7: 2087-2096, previously cited, Hartman et al., 2001, Science, 291: 1001-1004.

It is noted that this rejection was of record March 19, 2009 and is copied below for Applicant's convenience. Upon further consideration, the rejection applies to the instant claims.

As discussed above, Chattopadhyay et al. teach a method of generating genetically modified yeast comprising the steps of disrupting BTN1, conducting a microarray study to determine that HSP30 and BTN2 were upregulated, and disrupting HSP30 and BTN2 expression in BTN1 null yeast.

However, Chattopadhyay et al. do not teach that the modified expression step is inducible.

At the time of filing, Sauer teach that the cre-lox site-specific recombination system was shown to function in an efficient manner in yeast. The cre gene, which codes for a site-specific recombinase, was placed under control of the yeast GAL1 promoter. lox sites flanking the LEU2 gene were integrated into two different chromosomes in both orientations. Excisive recombination at the lox sites (as measured by the loss of the LEU2 gene) was promoted efficiently by the Cre protein and was dependent upon induction by galactose (Sauer, abstract).

Therefore, it would have been obvious to take the cre-lox system taught by Sauer and to flank the endogenous BTN1 sequence with lox sites. An artisan would have

Art Unit: 1632

done so in order to arrive at a yeast culture that can be split in half, wherein one half is induced with galactose. An artisan would then purify the mRNA from the galactose-induced and uninduced yeast and compared the mRNA expression between them in order to determine what genes were up- and downregulated following loss of BTN1 expression.

With regard to the claims being drawn to the genetic modification comprising introducing a vector which enable the at least one protein or protein fragment to be inducibly expressed (claim 26), it is noted that with regard to the limitation of “protein fragment” an artisan can design the loxP sites to excise almost the entire coding sequence of BTN1 such that only the 5' stump of BTN1 is expressed. With regard to the expression being inducible, it is noted that expression of the 5' stump of BTN occurs following induction of the cre-lox system.

With regard to claim 32 being drawn to the differentially expressed gene being less strongly expressed than in control organisms and the reduction or elimination of differential expression is carried out by enhancing expression of the differentially expressed gene, it is noted that while Chattopadhyay et al. focused on the two genes that were upregulated in BTN1 knockout yeast, an artisan would also have looked at genes that were downregulated in BTN1 knockout yeast in order to determine what effect(s) downregulated genes had on BTN1 knockout yeast. To do so, an artisan would have introduced a transgene construct overexpressing these downregulated genes. See for example, Hartman et al., 2000, who teach it would be desirable to study

Art Unit: 1632

buffering relationships (Hartman et al., page 1004, 1<sup>st</sup> col., under Mechanisms of Buffering).

With regard to claim 35 being drawn to a genetically modified yeast that expresses at least one foreign gene that results in compensating differential expression of at least one other gene endogenous to the modified yeast organism, it is noted that cre recombinase is a foreign gene and that upon disruption of BTN1 via cre-lox excision, HSP30 and BTN2 are upregulated, as shown by Chattopadhyay et al., abstract.

With regard to the claims being drawn to a method of identifying a substance having an effect on the function of a heterologously expressed protein or protein fragment (claim 36), it is noted that when the artisan provides the yeast comprising loxP sites flanking a region in the endogenous BTN1 sequence with galactose, that galactose is the substance that has an effect on the function of a heterologously expressed protein and that an artisan can easily measure the change (i.e., the presence or absence) of BTN1 following loxP excision with methods known in the art (e.g. PCR).

Thus, the claims are rejected.

Claims 24-26, 30-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi et al., 2000, FEBS Letters, 470: 156-160, previously cited, Gari et al., 1997, Yeast, 13: 837-848, previously cited, Wilson et al., 1999, PNAS, USA, 96: 12833-12838, previously cited, for reasons of record, December 11, 2009.

Applicant's arguments filed June 11, 2010 have been fully considered but they are not persuasive.

Applicant indicates that DeRisi et al. teach strains which show a detectable phenotype, which clearly constitutes a difference in the present invention. There is no restriction that the phenotype is proliferation. Applicant indicates that drug resistance as addressed in DeRisi et al. is included in the term of "behavior" as drug resistance results in the survival of a cell to which drug is administered (Applicant's emphasis, Applicant's response, pages 15-17). In response, this is not persuasive. With regard to Applicant indicating that the claims are not restricted to a phenotype being proliferation, Applicant is correct. However, as indicated in the Office Action, December 11, 2009, page 8, the claims are broadly written such that "phenotype perceptible from the outside" can be broadly read to be any phenotype, including overproliferation, a characteristic which the Pdr1p and/or Pdr3p yeast do not exhibit. Thus, the yeast described by DeRisi et al. meet the limitation of the claims with regard to "proliferation." In addition to this, the claims can broadly be read such that even after DeRisi et al.'s yeast expressed a transgene construct, the yeast continued to survive, even in media that contained a drug. As such, DeRisi et al.'s yeast would be readable on the claims because their phenotype of "survival" has not changed between growing yeast in normal media and drugged media. In addition to this, under normal culturing conditions, there is no difference between DeRisi et al.'s yeast and a wild type yeast; drug resistance is seen under a particular culturing condition. In this respect, DeRisi et al. meet the limitation of the claims.

Applicant indicates that with regard to the effects of a modification of expression of genes differentially expressed due to mutation in the *pdr1/3* genes (page 7, 2nd parag., page 8, 2nd parag. of the Office Action), no clear statement can be given as such subject matter is not examined in DeRisi et al. DeRisi et al. show that mutating *pdr1* and *pdr3* result in a perceptible change in phenotype (Applicant's response, page 18). In response, this is not persuasive. With regard to DeRisi et al. showing the effects of modification of expression of genes, DeRisi et al. teach that the expression of 23 other genes appeared to be repressed in the PDR1-3 and/or PDR3-7 mutants (DeRisi et al., abstract). With regard to Applicant indicating that there is a perceptible change in phenotype, it is noted that as discussed above, there is no change in phenotype in DeRisi et al.'s yeast as a) "phenotype" in the claims is broad for any phenotype and can be readable on a "phenotype" that is normal between wild type yeast and DeRisi et al.'s yeast; one type of phenotype that is the same between the yeast is cell-proliferation, b) the drug-resistance phenotype is not seen under normal conditions, and c) the fact that DeRisi et al.'s yeast survive media with drug is indicative that the yeast have not changed their phenotype.

Thus, the claims remain rejected.

### ***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-

272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Application/Control Number: 10/736,801

Page 15

Art Unit: 1632

/Joanne Hama/  
Primary Examiner  
Art Unit 1632